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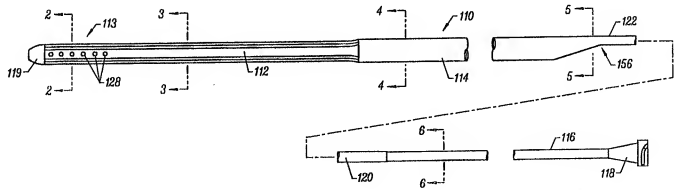

(57) Abstract

Restenosis in re-canalized blood vessels is inhibited by an antioxidant substance, such as probucol, intramurally at a target site within the blood vessel. Usually, the antioxidant substance is delivered using a catheter having infusion ports at its distal end. Optionally, the distal end of the catheter (110) is radially expanded to engage the infusion ports directly against the blood vessel wall. Delivery of the antioxidant substance may be effected before, during, or after the re-canalization procedure.

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LOCALIZED INTRAVASCULAR DELIVERY OF ANTIOXIDANT SUBSTANCES FOR INHIBITION OF RESTENOSIS IN RECANALIZED BLOOD VESSELS

The present application is a continuation of Provisional Application No. 60/034,693, filed on January 9, 1997, the full disclosure of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods for inhibiting restenosis in a blood vessel which may occur after an initial treatment for opening a stenotic region in the blood vessel. More particularly, the present invention relates to methods for the localized delivery of antioxidant substances for inhibition of localized intimal hyperplasia following balloon angioplasty and other interventional treatments.

Percutaneous transluminal angioplasty (PTA) procedures are widely used for treating stenotic atherosclerotic regions of a patient's vasculature to restore adequate blood flow. The catheter, having an expansible distal end usually in the form of an inflatable balloon, is positioned in the blood vessel at the stenotic site. The expansible end is expanded to dilate the vessel to restore adequate blood flow beyond the diseased region. While PTA has gained wide acceptance, it continues to be limited by two major problems: abrupt closure and restenosis.

The present invention is particularly concerned with methods for inhibiting restenosis which occurs as a result of intimal hyperplasia (excessive proliferation of the vessel intima) following balloon angioplasty and other anti-stenotic treatment protocols, such as atherectomy, laser angioplasty,

stent placement, and the like. Restenosis refers to the re-narrowing of an artery within weeks or months following an initially successful angioplasty or other primary treatment. Restenosis afflicts approximately up to 50% of all angioplasty patients and results at least in part from smooth muscle cell proliferation and migration. The biologic events initiating this smooth muscle cell activity are believed to be in part due to thrombin directly as well as indirectly through release products from platelets which have been recruited by thrombin. Patients suffering from restenosis will typically require further treatment.

Many different strategies have been proposed to reduce the restenosis rate, including mechanical (*e.g.*, prolonged balloon inflations during angioplasty, stenting, and the like) and pharmacological, (*e.g.*, the administration of anti-thrombotic drugs following angioplasty).

Pharmacologic treatment can be achieved either systemically or via localized intramural drug delivery. While systemic delivery is particularly easy to administer to the patient, it suffers from a number of disadvantages, including: 1) serious complications due to the activity of the agent at sites distant to the site of interest, 2) a large amount of agent is required to achieve therapeutic concentrations throughout the agent's volume of distribution, and 3) exposure of the agent to degradation and elimination by distant organ system. The localized delivery of drugs, in contrast, limits the total drug dosage required and provides site-specific activity where the drug has a much higher local concentration than is possible with systemic delivery.

Systemic and localized intravascular delivery of a variety of drugs have been proposed for the inhibition of restenosis following angioplasty and other primary intravascular treatments. The most common drugs suggested in the patent and medical literature include heparin, urokinase, streptokinase, tissue plasminogen activator (tPA), and the like. Other specific drugs and classes of drugs are listed in the references cited in the Background of the Art section below. To date, however, no one drug or combination of drugs

has proven to be entirely effective in inhibiting post-angioplasty restenosis. Thus, the need continues to identify specific drugs, drug administration protocols, and combinations of drugs and administration protocols which are more effective in at least some respects than the previous drugs and treatment protocols for inhibiting post-angioplasty restenosis.

Probucol is a well-characterized antioxidant drug which has been utilized by the treatment of atherosclerosis. See, for example Jackson et al., "Probucol and its mechanisms for reducing atherosclerosis," in: Malmendier et al., eds. *Hypercholesterolemia, Hypocholesterolemia, Hypertriglyceridemia in Vivo Kinetics*, New York, Plenum Press, 1990. The systemic delivery of probucol for inhibiting restenosis following angioplasty and other procedures has been demonstrated in animal models and humans, typically by delivering high doses of the drug prior to balloon angioplasty treatment.

The oral and systemic delivery of probucol must be continued for a significant period of time prior to angioplasty treatment in order to assure adequate drug concentrations in the tissue, including the neointimal, medial, advential and other perivascular structures.

For these reasons, it would be desirable to provide improved methods for inhibiting restenosis due to intimal hyperplasia and other reasons following angioplasty and other primary intervascular treatments. More particularly, it would be desirable to improve the delivery of probucol and other antioxidant substances to target sites within the blood vessels to be treated, either prior to, during, or following the recanalization procedure. Still more particularly, it would be desirable to demonstrate that the activity and effectiveness of probucol and other antioxidant substances are enhanced by localized intravascular delivery to target sites for angioplasty and other procedures.

2. Description of the Background Art

The systemic administration of probucol for the inhibition atherogenesis following balloon angioplasty has been demonstrated. See, for example, Scheider et al. (1993) Circulation 88:628-637, and Tardiff et al. (1996) Abstract 0524, Circulation 941-91. The use of anti-oxidants and/or free-radical scavengers for inhibiting restenosis is described in U.S. 5,326,757; WO 95/26193; and CA 2106695.

The use of intravascular catheters for delivering particular drugs and classes of drugs is described in U.S. Patent Nos. 5,180,366; 5,171,217; 5,049,132; and 5,021,044; and PCT Publications WO 93/08866 and WO 92/11895. Riessen et al. (1994) JACC 23:1234-1244 is a review article discussing the use of catheters and stents for the local delivery of therapeutic agents into the blood vessel wall.

A preferred infusion catheter for delivering antioxidant substance in accordance with the methods of the present invention is described in copending application serial no. 08/473,800, assigned to the assignee of the present invention, filed on June 7, 1995, the full disclosure of which is incorporated herein by reference. This copending application teaches that the catheter may be used for the intravascular delivery of anti-restenotic, anti-proliferative, thrombolytic, fibrinolytic, and other agents useful in connection with angioplasty treatment in a patient's coronary vasculature.

The intramural delivery of tissue factor pathway inhibitor for the inhibition of restenosis is described in copending application Serial No. 08/546,873, filed on October 23, 1995, naming Aaron Kaplan as the sole inventor and assigned to the assignee of the present application. The intramural delivery of vascular endothelial growth factor and other growth factors is described in copending application Serial No. _____ (Attorney Docket No. 15509-003110), filed on November 22, 1996, naming Aaron Kaplan as an inventor and assigned to the assignee of the present application.

SUMMARY OF THE INVENTION

The present invention provides methods for inhibiting restenosis which may result from intimal hyperplasia or other mechanisms in recanalized blood vessels. The methods comprise intramurally delivering an antioxidant substance to a target site within the blood vessel, either before, after, or during the recanalization procedure.

The term "restenosis" is defined as the recurrence of stenosis weeks or months after a corrective procedure has been performed at a target site within a patient's vasculature. Restenosis occurs in part as a result of intimal hyperplasia including smooth muscle cell proliferation and migration. The intramural delivery of antioxidant substances according to the present invention will inhibit restenosis. In particular, it is believed that the intramural delivery of anti-oxidants will reduce oxidative stress which initiates events which lead to restenosis.

The term "recanalized" is defined as the condition of the blood vessel after an initial corrective procedure has been performed to at least partially cure the stenotic condition. The "recanalized blood vessel" may be any blood vessel in the patient's vasculature, including veins, arteries, and particularly including coronary arteries, and prior to performing the initial corrective procedure, the blood vessel could have been partially or totally occluded at the target site. Usually, the corrective procedure will comprise an intravascular procedure, such as balloon angioplasty, atherectomy, stenting laser angioplasty, or the like, where the lumen of the treated blood vessel is enlarged to at least partially reverse a stenotic condition which existed prior to the treatment. Alternatively, the corrective procedure could involve coronary artery bypass, vascular graft implantation, endarterectomy, or the like.

The phrase "intramural delivery" is defined as localized delivery of the antioxidant substance into the blood vessel wall, including the neointimal, intimal, medial, adventitial and perivascular spaces, adjacent to the target site. Such intramural delivery will typically be effected

using an intravascular catheter, as described in greater detail below, but could also be achieved by the implantation of vascular implants capable of releasing a the antioxidant substance over time.

The phrase, "antioxidant substance" is defined to include a wide variety of antioxidant drugs which reduce oxidative stress when administered intramurally to a recanalized blood vessel. Preferred antioxidant substances will be small molecule drugs, typically having a molecular weight below 2,000D, usually being below 1500D, and more usually being below 1,000D. In particular, antioxidant substances according to the present invention include probucol, vitamin C, vitamin E, β-carotene, super oxide dismutase (SOD), Mn-SOD, polyethylene glycol-SOD, tirilazad, 1-banduronic acid and other biophosphonates, melatonin, α-tocopherol, thyme oil, procysteine (available from Transcend Pharmaceutical Company), glutathione, and notrone-related compounds. Presently preferred is the use of probucol.

The antioxidant substances can be formulated in a variety of conventional ways, including solutions, suspensions, gels, and the like. In some cases, it will be desirable to incorporate the antioxidants in time release compositions or structures. Usually, the antioxidant substances will be in a form suitable for delivery through a catheter. Alternatively, they may be incorporated into stents or other implantable, often erodible, structures.

In a first particular aspect of the present invention, the method for inhibiting restenosis in a recanalized blood vessel comprises advancing a distal end of the catheter to the target site within the recanalized blood vessel. An amount of the antioxidant substance sufficient to inhibit intimal hyperplasia at said site is then delivered through the distal end of the catheter, either before, during, or after the recanalization procedure. Usually, the catheter is introduced percutaneously to the patient's vasculature and advanced transluminally to the target site. The antioxidant substance is then delivered from a proximal end of the catheter, through a lumen in the catheter body, and to the

distal end from where it is released into the blood vessel wall. Optionally, the distal end of the catheter is expanded to engage infusion ports therein against the blood vessel wall to enhance intraluminal penetration.

In a second particular aspect of the present invention, the method for inhibiting restenosis in a recanalized blood vessel comprises advancing the distal end of an infusion catheter to a target site within the blood vessel, either before, during or after recanalization. The distal end of the infusion catheter is expanded to engage infusion ports therein against the luminal wall of the blood vessel, preferably by positioning a balloon within the distal end of the infusion catheter and inflating the balloon to a predetermined inflation pressure. An amount of the antioxidant substance sufficient to inhibit intimal hyperplasia at said target site is then delivered through the infusion ports, usually at a predetermined infusion pressure which is independent of the balloon inflation pressure.

In a third particular aspect of the present invention, a method for recanalizing a blood vessel comprises enlarging the blood vessel lumen at the target stenotic site. The distal end of an infusion catheter is advanced to the target site either before or closely following the enlarging step and an amount of the antioxidant substance sufficient to inhibit intimal hyperplasia or other cause of restenosis is then delivered through the distal end of the infusion catheter into the blood vessel wall. The enlarging step may comprise any conventional intravascular corrective procedure, such as balloon angioplasty, atherectomy, laser angioplasty, stent placement, endarterectomy and the like. The antioxidant substance may be delivered to the target site as a bolus, but will more usually be delivered in a continuous or discontinuous stream over an extended time period. The total amount of antioxidant substance delivered to the target site is typically in the range from 0.1 μg/kg to 10 mg/kg, more typically from 0.1 μg/kg to 1 mg/kg (body weight). When delivered continuously, the time period of delivery will usually be in the range from 0.1 minute to 360 minutes, more

usually being from 15 seconds to 5 minutes, although delivery times more than three minutes may require a delivery system that provides for blood perfusion to the distal vasculature. The time of delivery can be extended to one day to 50 weeks, or longer, when controlled release implanted devices, such as stents, endoluminal paving delivery, or timer release particles are employed.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a side view of a sleeve catheter incorporating drug delivery lumens useful in performing the methods of the present invention.

Figs. 2-6 are cross-sectional views taken along lines 2-6 in Fig. 1, respectively.

Figs. 7-9 illustrate the use of a balloon catheter to expand the distal end of the catheter of Figs. 1-6.

Figs. 10A and 10B are cross-sectional views of the distal region of the catheter of Fig. 1 shown in its non-expanded (Fig. 10A) and expanded (Fig. 10B) configurations.

Fig. 11 illustrates the use of the catheter of Fig. 1 to deliver a antioxidant substance to a coronary artery in combination with an angioplasty balloon catheter in accordance with the method of the present invention.

Fig. 12 is a cross-sectional view taken along line 12-12 of Fig. 11.

Fig. 13 is an alternative cross-sectional view similar to Fig. 12.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The methods of the present invention rely on the intramural delivery of an antioxidant substance to an intravascular target site to inhibit restenosis resulting from intimal hyperplasia or other causes following a conventional recanalization procedure.

Intramural deliver of antioxidant substances according to the methods of the present invention, may be accomplished using any of a variety of known intravascular drug delivery systems. Most commonly, the antioxidant

substance will be delivered using intravascular catheter delivery systems as described in greater detail below. In some cases, however, it may be advantageous to employ implanted devices, such as implanted stents capable of delivering the antioxidant substance for prolonged periods of time. See, for example, U.S. Patent No. 5,342,348 and EP 604 022, which describe stent apparatus capable of releasing a variety of drugs over time. Such stent apparatus would be suitable for intramural delivery of antioxidant substances according to the method of the present invention.

A variety of catheter systems useful for the direct intramural infusion of the antioxidant substance into the blood vessel wall are also well-described in the patent literature. Most commonly, balloon catheters having expandable distal ends capable of engaging the inner wall of a blood vessel and infusing the antioxidant substance directly therein are well-described in the patent literature. See, for example, U.S. Patent Nos. 5,318,531; 5,304,121; 5,295,962; 5,286,254; 5,254,089; 5,213,576; 5,197,946; 5,087,244; 5,049,132; 5,021,044; 4,994,033; and 4,824,436. Catheters having spaced-apart or helical balloons for expansion within the lumen of a blood vessel and delivery of a therapeutic agent to the resulting isolated treatment site are described in U.S. Patent Nos. 5,279,546; 5,226,888; 5,181,911; 4,824,436; and 4,636,195. A particular drug delivery catheter is commercially available under the trade name Dispatch™ from SciMed Life Systems, Inc., Maple Grove, Minnesota. Non-balloon drug deliver catheters are described in U.S. Patent Nos. 5,180,366; 5,112,305; and 5,021,044; and PCT Publication WO 92/11890. Ultrasonically assisted drug delivery catheters (phonophoresis devices) are described in U.S. Patent Nos. 5,362,309; 5,318,014; and 5,315,998. Other iontophoresis and phonophoresis drug delivery catheters are described in U.S. Patent Nos. 5,304,120; 5,282,785; and 5,267,985. Finally, sleeve catheters having drug delivery lumens intended for use in combination with conventional angioplasty balloon catheters are described in U.S. Patent Nos. 5,364,356 and 5,336,178. Any of the catheters described in the above-listed patents may

be employed for delivering antioxidant substances according to the method of the present invention. Full disclosures of each of these patent references are hereby incorporated herein by reference.

It would also be possible to deliver the antioxidant substance by applying a thin layer of a hydrogel or other polymeric carrier matrix to the endoluminal wall at the target location. Usually, the polymeric carrier will be biodegradable or bioeluting and serve as a temporary wall support while the antioxidant substance is released over time. Such endoluminal paving systems are described in, for example, U.S. Patent No. 5,328,471 and Slepian (1994) Card. Clin. 12:715-737.

The antioxidant substances used in the methods of the present invention will be incorporated into conventional pharmaceutical compositions for intramural delivery. In the case of continuous catheter delivery, the antioxidant substances will be incorporated into an acceptable fluid carrier, e.g., being formulated with sterile water, isotonic saline, glucose solution, or the like. The formulations may contain pharmaceutically acceptable auxiliary substances as are generally used in pharmaceutical preparations, including buffering agents, tonicity adjusting agents, such as sodium acetate, sodium lactate, sodium chloride, potassium chloride, and calcium chloride, and the like. The concentration of the antioxidant substance in the liquid formulation may vary widely, from 0.001% to 20%, typically being from 0.01% to 1% by weight. General methods for preparing such pharmaceutical formulations are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Philadelphia, Pennsylvania, 1985.

The pharmaceutical compositions will be delivered for a time sufficient to achieve the desired physiological effect, i.e., the partial or complete inhibition of intimal hyperplasia at the target site in the blood vessel. Generally, the total amount of the antioxidant substance delivered will be selected to be sufficient to inhibit intimal hyperplasia at the target site. Suitable total amounts based

on patient body weight will be from 0.1 μg/kg to 10 mg/kg, usually from 0.1 μg/kg to 1 mg/kg. These amounts can be delivered as a bolus, i.e., in a single amount released over a very short time period, typically on the order of seconds, but will more usually be delivered as a continuous stream (or discontinuous stream, e.g., a series of short pulses) of a fluid pharmaceutical formulation over time. The total amount of time will, of course, depend on the delivery rate and drug concentration in the fluid being delivered, typically being from 0.5 minute to 360 minutes, more usually from 1 minute to 120 minutes.

The pharmaceutical formulations delivered according to the methods of the present invention may include more than one antioxidant substance and/or other active agents in addition to the antioxidant substances. In particular, the formulations may include anti-coagulants and anti-thrombotic agents, such as heparin, low molecular weight heparin, and the like.

The methods of the present invention provide for the direct, intramural delivery of an antioxidant substance into the blood vessel wall. Preferably, the amounts of antioxidant substance released into systemic circulation will be sufficiently small so that there are no undesired systemic side effects.

Referring now to Figs. 1-6, a particular drug delivery catheter in the form of a sleeve infusion catheter 110 useful for delivering antioxidant substances according to the methods of the present invention will be described. Such infusion catheters are described in greater detail in copending application serial no. 08/473,800, filed on June 7, 1995, assigned to the assignee of the present application, the full disclosure of which has previously been incorporated herein by reference.

The infusion sleeve catheter 110 comprises a radially expansible infusion sleeve 112, a radially expansible portion 113 within the sleeve 112, a manifold section 114, and a shaft 116. A hub 118 is attached to the proximal end of the shaft 116 and may be connected to a source of infusion fluid,

such as a syringe, pump, or the like. An atraumatic tip 119 is secured to the distal end of the sleeve 112. Distal end 120 of the shaft is secured within a proximal tubular extension 122 of the manifold structure 114. As illustrated in Figs. 1-6, the shaft 116 is a metal hypo tube having a circular cross-sectional area. The length of the shaft will depend on the length of the other portions of the catheter 110, with the overall length of the catheter typically being about 90 to 150 cm for coronary applications introduced through the femoral artery, as described in more detail below.

The radially expansible infusion sleeve 112 comprises a central receptacle 114 (Figs. 2 and 3) and four infusion lumens 126. Infusion ports 128 are formed over the distal-most 2.5 to 10 cm of the expansible portion 113 of the sleeve 112. Usually, the expansible portion 113 of the sleeve is axially split along lines 132 (Fig. 2) to permit radial expansion, as illustrated in Fig. 9 described below. The distal ends of the lumens 126 will be sealed, typically by the tip 119. Other structures for providing radial expansibility are described above.

The manifold structure 114 comprises an outer sheath or tube 140 coaxially received over an inner tube 142. Annular lumen 144 directs infusate into the infusion lumens 126. The annular lumen 144 is connected to lumen 150 and shaft 116 (Fig. 6) by a crescent-shaped transition lumen region 152 (Fig. 5) which is formed near the balloon catheter entry port 156. The balloon entry port 156 opens into a catheter lumen 158, which in turn leads into the balloon receptacle 124, typically having a cross-sectional area in the range from 0.5 mm^2 to 2 mm^2, typically about 1.25 mm^2.

Referring now to Figs. 7-9, a balloon catheter BC having an inflatable balloon B may be introduced through entry port 156 so that the balloon B extends outward through the distal tip of the sleeve 112. The balloon may then be inflated and deflated while the infusion sleeve 112 remains retracted. After the balloon B is deflated, the sleeve 112 may be advanced distally over the balloon, as illustrated in

Fig. 8. By then inflating the balloon, the expansible portion 113 of the sleeve 112 will be expanded, as illustrated in Fig. 9.

The infusion sleeve 112 may have an alternative cross-section, as illustrated in Figs. 10A and 10B. The sleeve 112' may be formed with lumens 126' formed within the wall of the catheter, rather than on the outer surface of the catheter as illustrated in Figs. 1-9. The wall thickness in these constructions will typically be slightly greater, usually being in the range from 0.2 mm to 0.4 mm. The wall will be axially split along lines 132' in order to allow expansion, as shown in Fig. 10B.

Infusion catheter 110 may be introduced through conventional guiding catheter GC to position the infusion sleeve 12 within a coronary artery in the patient's heart H, as illustrated in Fig. 11. Guiding catheter GC may be any conventional guiding catheter intended for insertion into the femoral artery F, then via the patient's aorta A around the aortic arch AA, to one coronary ostia O. Such guiding catheters are commercially available through a number of suppliers, including Medtronic, Minneapolis, Minnesota, available under the tradename Sherpa™. Specific guiding catheters are available for introducing catheters to either the left main or the right coronary arteries. Such guiding catheters are manufactured in different sizes, typically from 7F to 10F when used for coronary interventional procedures.

According to the method of the present invention, the balloon catheter BC is introduced through the balloon entry port 156, as described previously in connection with Figs. 7-9. The atraumatic tip 119 of the infusion sleeve 112 will be positioned proximally of the balloon, typically by a distance in the range from 25 cm to 35 cm. The combination of the balloon catheter BC, and infusion catheter 110 will be introduced through the guiding catheter GC over a conventional guidewire GW until the balloon is positioned within the target site within the coronary artery. Preferably, the infusion sleeve 112 will remain positioned entirely within the guiding catheter GC while the balloon B of the balloon catheter BC is

initially located at the target site. The balloon may then be expanded to treat other regions within the coronary vasculature in a conventional manner. After the angioplasty treatment is completed, the infusion sleeve 112 will be advanced distally over the balloon catheter BC until the radially expansible portion is properly positioned over the balloon. Such positioning can be confirmed by proper alignments of radiopaque markers on the infusion sleeve 112 (not shown) with markers on the balloon catheter, typically within the balloon itself. After the infusion sleeve is properly positioned, the balloon B on the balloon catheter BC will be inflated to engage the infusion ports 128 against the inner wall of coronary artery.

The antioxidant substance is then delivered through the hub 118 for desired treatment. Typically, the antioxidant substance will be delivered at a flow rate from 10 ml/min to 40 ml/min, preferably from 20 ml/min to 30 ml/min. Infusion proximal pressures will typically be in the range of 30 psi to 150 psi, preferably from 70 psi to 110 psi. Balloon inflation pressures during infusion will typically be in the range from 0.5 atm to 6 atm, preferably from 1 atm to 2 atm. Specific treatment pressures, times, and other conditions will depend on the nature of the infusate and condition being treated. Typically, treatment periods will not exceed 5 mins., usually not exceed 3 mins. in order not to occlude the blood vessel for a longer time than is tolerable to the patient. Treatment protocols can be extended, however, by repetitively administering the infusate, *i.e.*, deflating the balloon to re-establish coronary perfusion and then re-inflating the balloon and delivering infusate after a time sufficient to perfuse the distal coronary tissue. Such delivery steps can be repeated two, three, or more times as necessary to achieve a desired effect.

As describe above, the infusion sleeve 112 was used to deliver the antioxidant substance after the balloon catheter BC was used to perform an angioplasty treatment within the blood vessel. Using the same catheter system, the infusion sleeve could also be used to deliver the antioxidant

substance prior to the angioplasty treatment. Note that the infusion treatment is performed at much lower balloon pressures than the angioplasty procedure. Thus, even though the same balloon is being used for expansion within the blood vessel, the delivery of antioxidant can be performed prior to any substantial injury to the blood vessel wall due to overstretching of the blood vessel wall by the angioplasty treatment. It will be further appreciated that delivery of the antioxidant substance could be performed using a separate catheter, either before or after recanalization by balloon angioplasty or other procedure. Use of the infusion sleeve 112, however, presents the additional possibility of delivering the antioxidant compound during a balloon angioplasty procedure. The infusion lumens 126 would have to be sufficiently reinforced to withstand the high angioplasty pressures, and the antioxidant solutions would have to be delivered under sufficient pressure in order to penetrate the blood vessel wall.

Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for inhibiting restenosis in a recanalized blood vessel, said method comprising intramurally delivering an antioxidant substance to a target site within the blood vessel, wherein the target site comprises a region that has or is to be recanalized.

2. A method as in claim 1, wherein the amount of the antioxidant is from 0.1 μg to 10 mg per kg of body weight.

3. A method as in claim 2, wherein the total amount of the antioxidant is delivered over a period in the range from 0.1 minute to 360 minutes.

4. A method as in claim 1, wherein the antioxidant substance is selected from the group consisting of probucol, vitamin C, vitamin E, β-carotene, super oxide dismutase (SOD), Mn-SOD, polyethylene glycol-SOD, tirilazad, 1-banduronic acid, melatonin, α-tocopherol, thyme oil, procysteine, glutathione, and notrone-related compounds.

5. A method as in claim 4, wherein the antioxidant is probucol.

6. A method for inhibiting restenosis in a recanalized blood vessel, said method comprising:

(a) advancing a distal end of a catheter to a target site within the blood vessel; and

(b) delivering through the distal end of the catheter into the blood vessel wall an amount of a an antioxidant substance sufficient to inhibit restenosis at said target site; and

(c) recanalizing the blood vessel at the target site, wherein the recanalizing step may occur before, during, or after delivery of the antioxidant.

7. A method as in claim 6, wherein the distal end of the catheter is introduced percutaneously to a patient's vasculature and advanced transluminally to the target site.

8. A method as in claim 6, wherein the antioxidant substance is delivered from a proximal end of the catheter, through a lumen in the catheter, to the distal end.

9. A method as in claim 6, further comprising expanding the distal end of the catheter to engage a plurality of infusion ports against the blood vessel wall, wherein the antioxidant substance is delivered through said infusion ports.

10. A method as in claim 6, wherein the amount of the antioxidant is from 0.1 μg to 10 mg per kg of body weight.

11. A method as in claim 10, wherein the total amount of antioxidant substance is delivered over a period in the range from 0.1 minute to 360 minutes.

12. A method as in claim 1, wherein the antioxidant substance is selected from the group consisting of probucol, vitamin C, vitamin E, β-carotene, super oxide dismutase (SOD), Mn-SOD, polyethylene glycol-SOD, tirilazad, 1-banduronic acid, melatonin, α-tocopherol, thyme oil, procysteine, glutathione, and notrone-related compounds.

13. A method as in claim 4, wherein the antioxidant is probucol.

14. A method for inhibiting restenosis in a recanalized blood vessel, said method comprising:

advancing the distal end of an infusion catheter to a target site within the recanalized blood vessel;

expanding the distal end of the infusion catheter to engage infusion ports on the catheter against the luminal wall of the blood vessel; and

delivering through the infusion ports into the blood vessel wall an amount of an antioxidant sufficient to inhibit restenosis following recanalization, wherein the recanalization may be effected before, during, or after delivery of the antioxidant.

15. A method as in claim 14, wherein the distal end of the catheter is introduced percutaneously to a patient's vasculature and advanced transluminally to the target site.

16. A method as in claim 14, wherein the antioxidant is delivered from a proximal end of the catheter, through a lumen in the catheter, to the infusion ports at the distal end.

17. A method as in claim 14, wherein the expanding step comprises:

positioning a balloon within the distal end of the infusion catheter; and

inflating the balloon to a predetermined inflation pressure.

18. A method as in claim 17, wherein the delivering step comprises supplying fluid to the infusion ports at a predetermined infusion pressure, wherein the inflation pressure is independent of the inflation pressure.

19. A method as in claim 14, wherein the expanding step comprises inflating the distal end of the infusion catheter having the infusion ports with a fluid carrying the antioxidant substance with an inflation pressure to release the antioxidant-containing fluid through the infusion ports.

20. A method as in claim 14, wherein the amount of the antioxidant substance is from 0.1 μg to 10 mg per kg of body weight.

21. A method as in claim 20, wherein the total amount of antioxidant substance is delivered over a period in the range from 0.1 minute to 360 minutes.

22. A method as in claim 14, wherein the antioxidant substance is selected from the group consisting of probucol, vitamin C, vitamin E, β-carotene, super oxide dismutase (SOD), Mn-SOD, polyethylene glycol-SOD, tirilazad, 1-banduronic acid, melatonin, α-tocopherol, thyme oil, procysteine, glutathione, and notrone-related compounds.

23. A method as in claim 22, wherein the antioxidant is probucol.

24. A method for recanalizing a blood vessel, said method comprising:

(a) enlarging the blood vessel lumen at a target site;

(b) advancing the distal end of an infusion catheter to the target site; and

(c) delivering through the distal end of the infusion catheter into the blood vessel wall an amount of an antioxidant substance sufficient to inhibit subsequent restenosis at said target site, wherein step (a) may be performed before, after, or during step (c).

25. A method as in claim 24, wherein the enlarging step comprises balloon angioplasty, atherectomy, laser recanalization, or stent placement.

26. A method as in claim 25, wherein the enlarging step comprises advancing an angioplasty balloon catheter to the treatment site, inflating a balloon at the distal end of the angioplasty balloon catheter to recanalize the blood vessel, and withdrawing the angioplasty balloon catheter.

27. A method as in claim 26, wherein the infusion catheter is advanced to the target site within one to ten minutes after withdrawing the angioplasty balloon catheter.

28. A method as in claim 26, wherein the infusion catheter is advanced to the target site and the antioxidant substance delivered prior to inflating the angioplasty balloon.

29. A method as in claim 26, wherein the delivering step comprises placing the infusion catheter over the balloon angioplasty catheter at the target site, inflating the balloon on the balloon angioplasty catheter to expand the distal end of the infusion catheter so that it contacts the blood vessel wall, and infusing the antioxidant material through the distal end of the infusion catheter while the balloon remains inflated therein.

30. A method as in claim 24, wherein the distal end of the infusion catheter is introduced percutaneously to a patient's vasculature and advanced transluminally to the target site.

31. A method as in claim 24, wherein the antioxidant substance is delivered from a proximal end of the catheter, through a lumen in the catheter, to the distal end.

32. A method as in claim 24, further comprising expanding the distal end of the catheter to engage a plurality of infusion ports against the blood vessel wall, wherein the antioxidant substance is delivered through said infusion ports.

33. A method as in claim 24, wherein the antioxidant substance is selected from the group consisting of probucol, vitamin C, vitamin E, β-carotene, super oxide dismutase (SOD), Mn-SOD, polyethylene glycol-SOD, tirilazad,

1-banduronic acid, melatonin, α-tocopherol, thyme oil, procysteine, glutathione, and notrone-related compounds.

34. A method as in claim 33, wherein the antioxidant is probucol.

35. A method as in claim 24, wherein the amount of the antioxidant substance is from 0.1 μg to 10 mg per kg of body weight.

36. A method as in claim 33, wherein the total amount of antioxidant substance is delivered over a period in the range from 0.1 minute to 360 minutes.

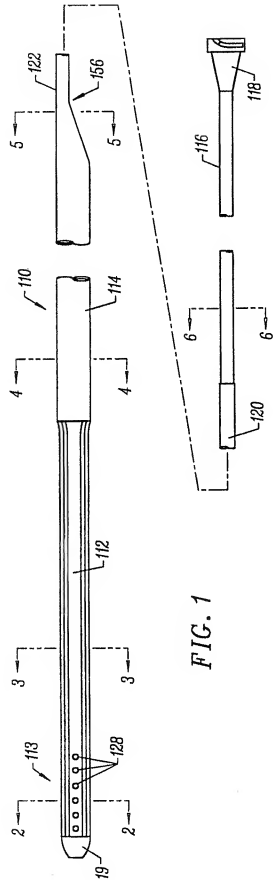

FIG. 1

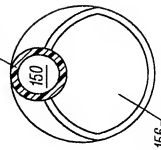

FIG. 6

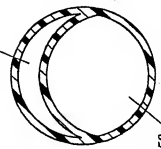

FIG. 5

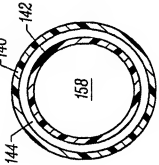

FIG. 4

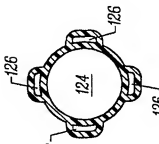

FIG. 3

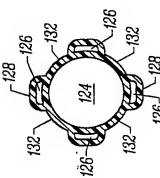

FIG. 2

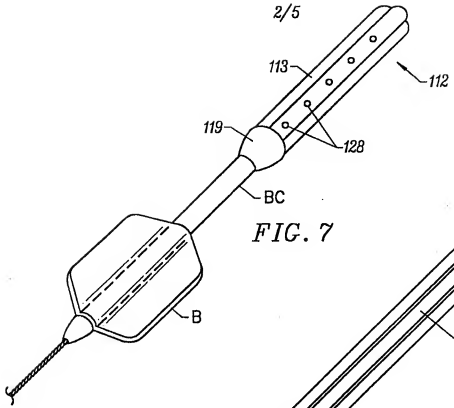

FIG. 7

FIG. 8

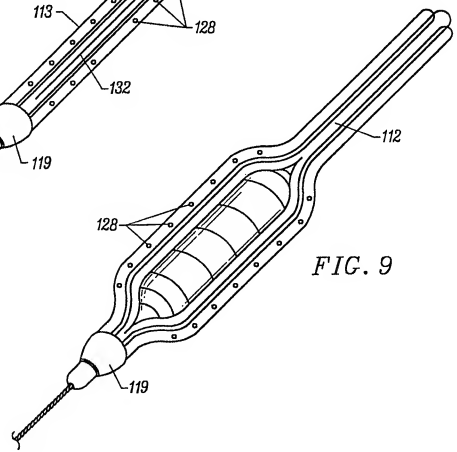

FIG. 9

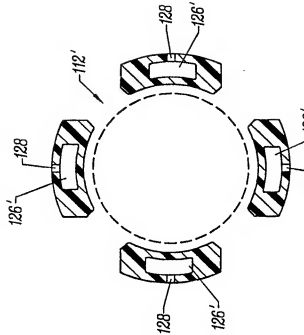

FIG. 10B

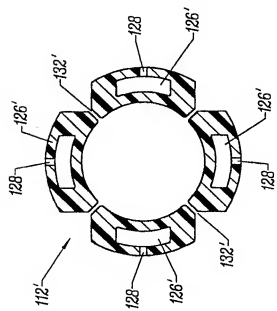

FIG. 10A

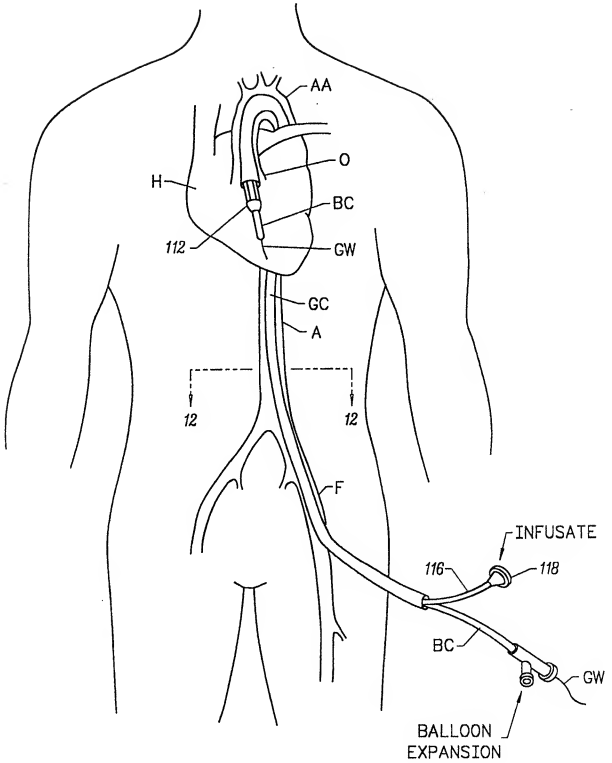
AA
O
H
BC
112
GW
GC
A
12
12
F
INFUSATE
116
118
BC
GW
BALLOON
EXPANSION

FIG. 11

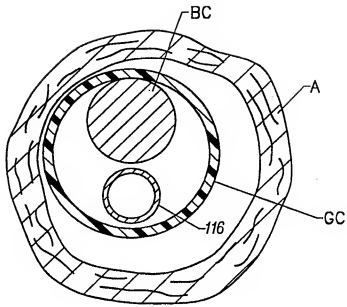

FIG. 12

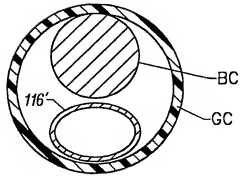

FIG. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00491

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61M 31/00
US CL :604/45

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/49, 96, 280

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,584,804 A (KLATZ ET AL) 17 DECEMBER 1996, ENTIRE PATENT.	1-36
Y	US 5,573,772 A (DOWNEY ET AL) 12 NOVEMBER 1996, ENTIRE PATENT.	1-36

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevence	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
22 JUNE 1998	20 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer MANUEL MENDEZ
Facsimile No. (703) 305-3230	Telephone No. (703) 308-2221